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# ETIOLOGY AND PATHOGENESIS OF CANCER IN THE LIGHT OF IMMUNOLOGICAL EXPERIMENTATION

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During the past few years the study of the etiology of malignant tumors has disclosed many important facts which cast light on those aspects of this problem which have continued to remain obscure over a long period of time. It is well known that, of the numerous theories dealing with cancer, the most intensively developed during the past decade have been the chemical and virus theories.

The chemical theory arose a long time ago as a result of observations on occupational cancer and has led to an accumulation of a tremendous amount of data, which seem to prove beyond any doubt the role of chemical substances in the formation of tumors. At present, there are known many chemically pure, synthetic substances, the introduction of which into the organism of animals leads to the formation of tumors. The cancerogenic activity of some of them (e.g. dimethylbenzanthracene, methylcholanthrene) is so high that even a single dose of a fraction of a milligram results in the formation of a tumor. Belief in the chemical theory has grown especially since it was determined that cancerogenic substances can be formed in the organism from the normal products of cellular metabolism and since substances of this kind have been extracted from cancerous tissue (Shabad).

However, the chemical theory of the origin of tumors has met with a number of difficulties which it has been unable to overcome. During the course of study of the factors leading to the formation of tumors, the number of difficulties has continued to increase. It developed that, aside from cancerogenic substances, cancer can develop as a result of the action of radium, Roentgen, or ultraviolet rays; upon the introduction into the organism of sex hormones, arsenic, or distillates of tobacco and coffee; upon repeated burns; upon the penetration into the tissues of certain worms; as a result of ulcers and erosion; after prolonged mechanical irritation; and even after repeated introduction of glucose and fructose.

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It is obvious that substances and irritations which vary as widely as these cannot all be the direct cause of cancer. Thus, the chemical theory of the origin of tumors could not serve as a rational explanation for the extraordinary variety of factors, the action of which on the organism is followed by the inception of cancer.

Attempts to transform a normal cell into a cancerous one through the action of cancerogenic substance in tissue cultures have proved unsuccessful. Even a very prolonged action of such an active cancerogenic substance as methylcholanthrene does not result in the formation of tumor cells in tissue cultures, i.e., cells which upon implantation into the organism would have induced development of a tumor. If cancerogenic substances actually serve as the etiological factor in cancer, they should transform a normal cell into a tumor cell, i.e., have an effect similar to viruses on cells in tissue cultures.

The virus theory has also encountered difficulties. First stated by Mechnikov and Borrel prior to the discovery of tumor viruses this theory developed very slowly, meeting with complete apathy on the part of the medical world. However, facts obtained in the study of cancer from the point of view of the virus theory attracted increasing attention and at present the virus theory is of interest to the widest circle of physicians.

Most pertinent have been facts obtained in the study of cancer of the lactic glands of mice. The stimulus in this disease proved to be a special virus transferred with the milk from the mother to its young. Mice are sensitive to this virus only during the first 2-3 weeks of their lives. Even when a very large quantity of this virus is introduced into a mature mouse, the animal does not develop cancer, though it remains a carrier of the virus throughout its entire life. A necessary condition for becoming diseased through the introduction of the virus into the organism is pregnancy. A mouse that has not been fertilized does not get cancer, even though it has received the virus during the first few weeks of its life.

All these data attest to the fact that the virus of cancer of the lactic glands of mice is only very slightly pathogenic. A number of conditions are required for it to manifest its action.

At present, there are numerous tumor-producing viruses which are reliably known to cause tumors also in other animals, such as rabbits, chickens, ducks, frogs, and fish. The majority of these tumors had to be photographed with the help of the electron microscope, while a few of them, including cancer of the lactic glands of mice, are visible under the optical microscope (Morozov, Baydakova). As other viruses, tumor viruses in the majority of cases are spherical in shape and resemble the coccus forms of bacteria. However, there are relatively few tumors whose virus etiology has been reliably established. In the majority of tumors, both in humans and in animals, no viruses capable of causing the formation of such tumors could be found. This fact is the main obstacle to the universal acceptance of the virus theory.

The inability to isolate viruses from the majority of tumors has been variously explained. It is known that it is easy to obtain the virus serving as the inducer of rabbit papilloma. However, as soon as the papilloma becomes malignant, the virus can no longer be detected; it assumes what is known as a "masked" form. Similar masking is known for other infectious viruses. Thus, the influenza virus, upon combining in the form of complex compounds with certain enzymes, completely loses its activity and regains it only after the breakdown of the complex. It is possible that failures to isolate viruses from the majority of tumors are thus due to the fact that the viruses are present in a masked form.

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It is also possible that a special method not yet discovered would be required to isolate viruses from the majority of tumors. The special characteristics of the virus of cancer of the lactic glands, which can be isolated only under certain conditions are pointed out above. The method by which this virus was detected has not yet been applied to the study of other tumors and it is possible that with the help of this or of some other method, other viruses as well will be isolated. The advantage of applying this method of research has been confirmed by a recent communication by Yablonovskaya, who, by using the chorioallantois membrane of the chicken embryo as a medium, isolated a virus-like agent from several tumors of the central nervous system.

All the reasons cited to explain the lack of success in isolating viruses from the majority of tumors are based on experimental data. But these reasons are still merely conjectural. If viruses serve as etiological factors for tumors and are actually contained in them, even though in a masked form, they should be detectable in cancers as a foreign protein. Actually, each virus is made up principally of protein which is foreign to the organism in which the virus has developed. Under such circumstances, when the virus cannot be detected by its pathogenic action as a biological agent, the protein substance of which the virus is composed should be detectable by immunological reactions as an antigen foreign to the organism. Immunological reactions are the most sensitive of all reactions known up to now, disclosing the presence of proteins and determining their specific nature. It is for this reason that they are widely used in forensic medicine for an exact determination of type attributes of blood and other proteins.

Consequently, it would be quite natural to try to eliminate those obstacles which are encountered by the virus theory of the origin of cancer by means of immunological experimentation.

Over the course of many years, our attempts to find in tumors which are not transmitted by filtrates any sort of foreign protein have not met with success. Our failure, as later research showed, was due to the small concentration of this protein in tumors and to insufficient sensitivity of the usual immunological reactions. Inasmuch as viruses basically consist of nucleoproteids, we studied nucleoprotein fractions from tumor tissues, hoping that they would contain more of the tumor virus than the entire mass of tumor tissue. With the help of the complement-fixation reaction and of precipitation, we were able to establish the presence of a specific tumor antigen in these fractions.

However, as shown by experiments with tumors in which the virus is easily detected by means of a biological test (chicken sarcoma), the nucleoprotein fractions of tumor tissue as well as the substance of the tumor virus also contained protein substances of normal tissue. For this reason, the results obtained would not permit a clear and infallible differentiation between qualitative characteristics of antigens from tumorous cells and antigens of normal cells.

Inasmuch as attempts to obtain the virus protein in a form sufficiently free of proteins from normal tissue proved fruitless, we developed a special reaction which came to be called the reaction of anaphylaxis with desensitization; this reaction permitted the detection of the specific substances of tumors even when found in a mixture with proteins from normal tissue.

The nature of the reaction is as follows. Guinea pigs are injected subcutaneously with a fixed number of milligrams of the nucleoprotein fractions obtained from tumor tissue, e.g., from cancer of the liver. It is known that guinea pigs who receive a certain protein parenterally become highly sensitive to it and respond by means of an anaphylactic shock to its repeated injection. If the guinea pigs survive this shock, they do not react to any further introduction of this particular protein. In other words, the first injection of protein sensitizes them, while repeated injection (if they survive) desensitizes them to this protein.

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Upon having received a nucleoproteid fraction from a cancerous liver, a guinea pig becomes highly sensitive to the injection of nucleoproteid. Similar experiments show that it is sensitive even to nucleoproteid from a healthy liver. To learn whether a nucleoproteid from a cancerous liver contains a substance absent from a nucleoproteid fraction of a healthy liver, the following procedure is employed. A guinea pig sensitized with a cancerous fraction can be desensitized by a fraction removed from normal tissue. After this, it should not react to a nucleoproteid fraction from normal tissue. In order to test this hypothesis this fraction is once more introduced into the guinea pig, but this time in a larger dose.

If this test for the full degree of desensitization proves successful and if the guinea pig does not react to the final increased test dose, it is given a nucleoproteid fraction from cancerous tissue, in the given case from cancerous tissue, in the given case from cancerous liver, in a dose which does not exceed the dose used in testing for the full degree of desensitization. As a rule, the guinea pig responds characteristically to this, sometimes by a fatal anaphylactic shock. This seemingly attests to the fact that there is a substance in tumor tissue which is absent from normal tissue.

These experiments, carried out together with a number of my colleagues (Nartsissov, Baydakova, Parnes, Gorodilova, Shershul'skaya, Radzikhovskaya, Freyman, Gardash'yan, Avenirova, etc.), showed that the reaction of anaphylaxis with desensitization discloses specific substances in all investigated tumors. At present, they have been disclosed in man in tumors of most varied localizations, in tumors of monkeys induced by a cancerogenic factor, and in various tumors of rabbits, rats, mice, and chickens. These include both spontaneous and induced as well as transplanted tumors.

The tremendous amount of material which has accumulated concerning this question at the Institute imeni N. F. Gamaleya and the Central Oncological Institute imeni P. A. Gertsen is supplemented by the findings of Dyad'kova (Institute of Oncology of the Academy of Medical Sciences USSR), which disclose the presence of a specific substance in induced tumors of chickens, and also the findings of Rapoport (Institute of Neurosurgery imeni N. N. Burdenko), who was the first to discover the specific substance in tumors of the central nervous system. Finally, there was recently published the work of Ginzburg and her colleagues, Ioffe, Rozental', Larionov, Smoylovskaya, and Medvedev, who also detected the specific substance in tumors with the aid of the reaction of complement fixation.

It is necessary to point out that a special commission of the Academy of Medical Sciences USSR composed of L. M. Shabad, N. N. Zhukov-Verezhnikov, M. M. Mayevskiy, P. N. Kosyakov, N. N. Medvedev, and others made a special check of our investigations disclosing the specific substance in tumors, and completely verified our results.

Thus, this question, the study of which was begun by us as early as 1936, may be considered to be conclusively resolved. Malignant tumors contain protein substances (specific antigens) which are absent from normal tissues.

What are these antigens? Are they virus substances, the detection of which is the problem of our researchers, or, possibly, are they a special protein created as a result of disruption of the process of synthesis occurring during cancer? The possibility of such disruption and the creation of a special tumor protein was confirmed by a number of studies by V. I. Zbarskiy.

The problem of the nature of specific antigens of tumors proved to be very complex and cannot be considered as having been solved yet. However, the data obtained lead to a number of premises most essential for considering the pathogenesis of tumors.

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First of all, there was investigated the question whether the virus contains specific antigens /whether the specific antigens contain virus?/ when the antigens are being given off by a tumor the virus etiology of which has been definitely established. Corresponding experiments (Radzikhovskaya) have shown that even 0.005 milligram of a specific antigen removed from chicken sarcoma contains an active virus which is capable of producing the same tumor.

In this way, the method we utilized in removing nucleoprotein fractions, actually permits the extraction of the virus protein in a concentrated form if the virus is contained in the tumor. This has been confirmed by experiments on the immunization of animals with specific antigens from tumors. Experiments in which rabbits, chickens, and mice were immunized with specific antigens obtained from rabbit papilloma, chicken sarcoma, and cancer of the lactic glands of mice (Baydakova, Vadova, and Radzikhovskaya) showed the undoubted effectiveness of such immunization.

All these data permit us to state with certainty that specific antigens filtered from tumors actually contain a protein which is a virus substance.

A rather important factor, making it possible to extend this conclusion to specific antigens from tumors in which viruses were not directly discovered, was the precise establishment of the fact that these antigens were foreign to the organism from the tumor of which they were removed (Nartsissov).

It is difficult to grant, for example, that the human organism can synthesize a nonhuman protein, one which is foreign to it. In cases where such a protein was detected, it was always the protein of a infectious agent which had penetrated into the organism from outside.

However, there are also known cases of disruption of protein synthesis in the organism when there is being synthesized not a foreign protein but one differing from the normal and normally absent from the organism. This process occurs, for example, in the formation of antibodies. The antigen entering a cell of the reticulo-endothelium disrupts the synthesis of globulins while the modified globulins being formed in this connection are antibodies.

It would be quite natural to raise the question whether there do not also enter into the composition of the specific tumor antigens detected by us modified globulins of the organism which could be produced as a result of the action of the virus on the cell and disruption by the virus of the processes of synthesis. At present, we have obtained in our laboratory a number of indirect data giving evidence of such a possibility.

In studies making use of the reaction of anaphylaxis with desensitization for nucleoprotein fractions, investigation of amyloid spleens of patients who died of tuberculosis disclosed that there are contained in the spleens three types of antigens: a species and organ antigen, a tuberculous antigen, and an amyloid antigen. The amyloid antigen is absent from the spleens of healthy persons but it has been found in the spleens of persons who died from chronic sepsis.

These data show that the pathological process can induce a disruption of metabolism in the organism which is accompanied by the synthesis of modified proteins different from those of a normal organism.

It is quite probable that a comparable process also takes place in cancer. The cell which is affected by the tumor virus preserves for a long time the character of its protein synthesis, but there comes a time when the regulatory functions prove inadequate, the synthesis of the protein is modified, and there is produced in the cell a protein which differs from the normal.

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Fundamentally, this is evidently the malignant process. Regulatory devices of the organism directed by the central nervous system prove inadequate for the cells with modified protein and for this reason a progressive growth of these cells begins, resulting in the formation of a tumor.

It is quite probable that starting from the moment of the formation of cancer protein the role of the virus changes considerably. In as far as the virus induces the indicated change in metabolism, it is possible to hold that it has a special affinity to the cancerous protein and is blocked by it in the same way that the antigen is blocked by the antibody formed as a result of the change in metabolism in the cells induced by this antigen. However it may be, the formation of a cancer protein as a result of the action of the virus on the cell represents one of the most important steps in the pathogenesis of cancer.

If need not be remarked that what has been stated above is only a working hypothesis developed during the course of our experiments. Hypotheses of this type are necessary in studying such a complex problem as that of the etiology and pathogenesis of cancer. Nevertheless, we would not have decided to formulate it if, on the one hand, we did not have the above-described indirect data on which this hypothesis could be based and, on the other hand, if we did not see the way to check it experimentally. Further investigation will make it possible either to confirm or to reject it.

At present, it is important that this hypothesis opens up to us new possibilities for the study of cancer.

Our experiments of preceding years definitely established that immunity to the tumor virus and immunity to the tumor cell are dependent on different mechanisms. This position was recently confirmed in the experiments of Radzikhovskaya with chicken sarcoma. With considerable certainty, we now can assume that this mechanism in the first case is directed at the neutralization of the virus antigen and in the second case to the neutralization of the antigen of the cancer protein. Since the problem of obtaining an artificial immunity to the tumor virus may now be considered as having been resolved in principle, we can broach the task of producing an artificial immunity to tumor cells by utilizing antigens of the cancerous protein. These still limited data which we now have at our disposal and which pertain to two different tumors make it possible to think not only of the considerable instability of such antigens but also of the possibility of still producing an artificial immunity to the cancer cell. It is hardly necessary to speak of the tremendous practical significance of an exhaustive solution to this problem.

What has been described above makes possible the following brief formulation of a hypothesis concerning the origin of cancer. Tumor viruses penetrate into the organism from without. The manner of this penetration has so far been studied for two kinds of tumors: rabbit papillomae, the virus of which is transmitted by ticks, and cancer of the lacteal gland of mice, the virus of which is transmitted by milk. Tumor viruses entering the organism do not manifest their disease-producing power for a very long time. This is because of weakness of the disease-producing power for the great majority of such viruses and the necessity for the fulfillment of a number of conditions for its manifestation.

One of the principal conditions is the creation in the organism of centers of cell proliferation. This is the manner in which numerous carcinogenic substances and reactions exert their action. In spite of the wide variety of their nature, all of them induce proliferating processes and metaplasia of tissue resulting in the formation of a large number of young, not completely typical, cells. Thus, all these cancerogenic substances and reactions are not etiological but pathogenetic factors. They create in the organism conditions in which the already present virus can manifest its pathogenic activity.

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The virus, having penetrated into the proliferating cells, disrupts the process of metabolism taking place in them and thus modifies the synthesis of protein. As a result of this, cells are produced with a protein which differs from the normal. This is basically the process of malignant growth. Inasmuch as the instruments regulating the growth of cells were created in the process of evolution with respect to cells with normal protein, they prove to be inadequate in regard to cells whose protein has been modified and has become cancerous. For this reason an intensified multiplication of these cells begins, resulting in the formation of a tumor.

The virus, having disturbed the synthesis of protein in the cell, in the majority of cases is blocked by the newly formed protein and for this reason cannot be detected in the tumor by the usual methods.

This hypothesis considers the origin of a tumor as a complex chain process. Certain links in this process are accessible to immunological analysis at present, thanks to our research and can be artificially inactivated by immunological reactions.

The basic problem of further research consists in the immunological study of the process of malignant growth and the artificial creation of immunity to the tumor cell.

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